FORM PTO-1390 (REV 11-98)

U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: Le A 32 842

U S APPLICATION NO (If known see 37 CFR 1 5): 09/700320

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/02969	03 May 1999 (03.05.99)	15 May 1998 (15.05.98)

TITLE OF INVENTION: EFFERVESCENT PREPARATIONS

APPLICANT(S) FOR DO/EO/US: WALTER, Reinhard and OHAGE-SPITZLEI, Petra

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND or SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(l).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information: **1) Certificate of Mailing under 37 C.F.R. 1.10;**

    2) Transmittal of Information Disclosure Statement under 37 C.F.R. 1.97(b);

    3) Information Disclosure Citation (Modified Form PTO-1449) and references cited therein; and

    4) Return Receipt Post Card.

Date of Deposit: NOV 14 2000
Express Mail Label No. EK662536974US

529 Rec'd PCT/PTC 14 NOV 2000

U.S. APPLICATION NO (if known, see 37 CFR 1.5) 09/700320 | INTERNATIONAL APPLICATION NO PCT/EP99/02969 | ATTORNEY'S DOCKET NUMBER Le A 32 842

17. [X] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5))

		CALCULATIONS PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	**$970.00**	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	**$840.00**	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	**$760.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)	**$670.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)	**$96.00**	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$ 860.00
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(c)).		$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	7 -20 =	0	X $18.00	$ 0.00
Independent claims	2 -3 =	0	X $78.00	$ 0.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+$260.00	$ 0.00
TOTAL OF ABOVE CALCULATIONS =				$ 860.00
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).				$ 0.00
SUBTOTAL =				$
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$
TOTAL NATIONAL FEE =				$ 860.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 0.00
TOTAL FEES ENCLOSED =				$
			Amount to be: refunded	$
			charged	$

a. [ ] A check in the amount of $_____ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 13-3372 m the amount of $ 860.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3372 A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

Jeffrey M. Greenman
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Jerrie L. Chiu
SIGNATURE

Jerrie L. Chiu
NAME

41,670
REGISTRATION NUMBER

Attorney's Docket No. Le A 32 842

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Walter, et al.

Serial No.: National Stage Filing of PCT/EP99/02969

Filed: herewith

For: Effervescent Preparations

BOX PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 CFR 1.10

I hereby certify that the *attached* correspondence comprising:

- Transmittal Letter to the United States Designated/Elected Office (DO/EO/US) Concerning a Filing under 35 U.S.C. 371 [IN DUPLICATE];
- A First Preliminary Amendment;
- Combined Declaration and Power of Attorney (35 U.S.C. 371(c)(4);
- English translation of the International Application (35 U.S.C. 371(c)(2));
- Copy of the International Application as filed (35 U.S.C. 371(c)(2));
- Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98 consisting of Transmittal of Information Disclosure Statement, Information Disclosure Citation (Modified Form PTO-1449), and copies of references cited therein; and
- Return Receipt Post Card.

is, on the date shown below, being deposited with the United States Postal Service, in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EK662536974US, addressed to:

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Assistant Commissioner for Patents
Washington, D.C. 20231

NOV 14 2000
Date

Signature of Person Certifying / Beatriz Alviz

Atty. Docket No.: Le A 32 842

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Walter, *et al.*

SERIAL NO.: National Stage Filing of PCT/EP99/02969

FILING DATE: Herewith

TITLE: Effervescent Preparations

PRELIMINARY AMENDMENT

Box PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Preliminary Amendment is submitted in the above-captioned national stage application of PCT/EP99/02969 filed on even date herewith. Please amend the application as follows:

In the Claims

Please amend claims 1, 2 and 7 as follows:

1. (Amended) Process for producing medicament-containing effervescent preparations [consisting of] comprising

A. effervescent composition [containing] comprising

(i) CO_2 donor and

(ii) acidic component,

B. pharmaceutical active substance and

C. ancillary substance,

[characterized in that] wherein

- at least one of the two components A(i) and A(ii) [and, where appropriate, other effervescent preparation components] are dispersed in molten C) sugar and/or sugar alcohol and/or sugar substitute, [and the resulting mixture is tabletted where appropriate].

2. (Amended) Process according to Claim 1, wherein

- a melt [consisting of] comprising component A(i) and/or A(ii) and C) fusible sugar, sugar alcohol and/or sugar substitute is comminuted during or after the cooling,

- the comminuted product is mixed with active substance B, with component (i) or (ii), which is still missing [where appropriate,] of the effervescent composition A [and, where appropriate, with further ancillary substances C] and, [where appropriate,]

- the resulting mixture is tabletted.

7. (Amended) Effervescent preparation [consisting of] comprising

A. effervescent composition [containing] comprising

(i) CO_2 donor and

(ii) acidic component,

B. pharmaceutical active substance and

C. ancillary substance,

[characterized in that] wherein ancillary substance C contains fusible sugar and/or sugar alcohol and/or sugar substitute, and component A(i) and/or A(ii)

is dispersed in a matrix of fusible sugar and/or sugar alcohol and/or sugar substitute.

Remarks

Claims 1-7 are pending. By way of this Preliminary Amendment, claims 1, 2 and 7 have been amended. These claim amendments are being made solely for purposes of placing the claims in the appropriate format for U.S. prosecution.

Applicants believe that the subject matter of the pending claims is patentable and that the instant application should accordingly be allowed. If the Examiner believes that a conversation with Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned attorney at (203) 812-3964.

Respectfully submitted,

Dated: Nov. 14, 2000

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Effervescent preparations

The invention relates to a process for producing medicament-containing effervescent preparations with at least partial melting of a preparation component and to effervescent preparations obtainable by this process.

Effervescent preparations such as, for example, effervescent powders or effervescent tablets are a formulation form, for example for active substances with a long absorption time or with a tendency to irritate the gastric mucosa, which is able to mitigate the disadvantageous properties mentioned for the active substances. Medicament-containing effervescent preparations therefore enjoy increasing popularity. They are normally produced in 3 to 4 stages, namely by

a) granulating the effervescent composition consisting of CO_2 donor and CO_2-releasing acidic component,
b) mixing the other components (active substances and other ancillary substances),
c) combining the components obtained from process steps a) and b) and, where appropriate,
d) tabletting the mixture obtained in step c).

Since both the CO_2 donor and the acidic component are relatively unsuitable for direct tabletting, the components of the effervescent composition have in the past been subjected, where appropriate in combination with the active substance, to a granulation process before the tabletting; compare, for example, German Offenlegungsschrift 22 16 072. The stability of the effervescent tablets produced in this way is, however, still unsatisfactory. The additional use of buffer substances and flavourings (which, after all, usually consist of many individual different compounds) in particular results in a sensitivity to water which leads, on storage, to discoloration, distension and degradation reactions. To avoid these unwanted reactions, effervescent preparations are often sealed in metal foils. Although this measure extends the shelf life, it is not possible reliably to prevent distension of the metal foil sachets on prolonged storage.

It has now been found, surprisingly, that the stability of medicament-containing effervescent preparations can be increased by a process in which a preparation component is melted.

The invention thus relates to a process for producing medicament-containing effervescent preparations consisting of

A. effervescent composition containing
   (i) CO_2 donor and
   (ii) acidic component,
B. pharmaceutical active substance and
C. ancillary substance,

characterized in that

at least one of the two components A(i), A(ii) and, where appropriate, other effervescent preparation components are dispersed in molten C) sugar and/or sugar alcohol and/or sugar substitute, and the resulting mixture is tabletted where appropriate.

The invention entails dispersing where appropriate one, a plurality or all of the remaining effervescent preparation components in the melt.

A preferred process is characterized in that

- a melt of component A(i) and/or A(ii) and C) fusible sugar and/or sugar alcohol and/or sugar substitute is comminuted during or after the cooling,
- the comminuted product is mixed with active substance B, with component (i) or (ii), which is still missing where appropriate, of the effervescent composition A and, where appropriate, with further ancillary substances C and, where appropriate,
- the resulting mixture is tabletted.

Preferred CO_2 donors A(i) comprise alkali metal and alkaline earth metal carbonates and bicarbonates, especially sodium and potassium carbonates and bicarbonates, and magnesium and calcium carbonates.

Suitable as acidic component A(ii), which liberates carbon dioxide from the CO_2 donor A(i), are all physiologically acceptable acids (so-called "acidulants"), which are strong enough to liberate carbon dioxide from component A(i); such acids have a first equilibrium exponent pKa of from 1 to 7, preferably 2 to 6 (at 25°C). Preferred acidic components A(i) comprise ascorbic acid and polybasic carboxylic acids

having 3 to 8, preferably 4 to 6, C atoms and 2 to 4 carboxyl groups per molecule, such as, for example, vitamin C, malic acid, citric acid, tartaric acid and mixtures thereof.

Suitable pharmaceutical active substances C comprise
analgesics such as ibuprofen, ketoprofen, paracetamol, acetylsalicylic acid, COX_2 inhibitors such as nimesulide, meloxicam, naproxen, propyphenazone, metamizole,
antacids such as hydrotalcite, magaldrate, calcium carbonate,
antiasthmatics/bronchospasmolytics such as salbutamol, tulobuterol, terbutaline, cromoglicic acid, ketotifen, theophylline,
antibiotics such as quinolones, tetracyclines, cephalosporins, penicillins, macrolides, sulphonamides, polypeptides,
phychopharmaceuticals such as benzodiazepines, haloperidol, amitryptyline, carbamazepine,
antirheumatics such as phenylbutazone, indometacin, diclofenac, piroxicam,
antidiabetics such as metformin, glibenclamide, acarbose, glisoxepide,
antiallergics/antihistamines such as astemizole, terfenadine, loratadine, clemastine, bamipine, cetirizine,
antihypotensives such as etilefrine, norfenefrine, dihydroergotamine mesilate,
antitussives such as codeine, dextromethorphan, clobutinol, dropropizine,
antihypertensives such as beta blockers such as propranolol, atenolol, metoprolol, prazosin,
antihypertensives such as calcium channel blockers such as nifedipine, nitrendipine, diltiazem, verapamil, felodipine, nimodipine,
laxatives such as sodium picosulphate, lactulose, lactitol,
mucolytics/expectorants such as ambroxol, bromhexine, guaifenesin, acetylcysteine, carbocisteine,
H2 blockers such as ranitidine, famotidine, pirenzepine,
local anaesthetics such as benzocaine, lidocaine, procaine,
antiemetics/prokinetics such as metoclopramide, domperidone, meclozine, dimenhydrinate,
lipid lowering agents such as fenofibrate, bezafibrate, pravastatin, fluvastatin,
agents effective for migraine, such as caffeine, dihydroergotamine, ergotamine, sumatriptan, pizotifen,
sympathomimetics such as pseudoephedrine, pholedrine,
vitamins and minerals.

The ancillary substances C, which should melt at least partially in the process according to the invention, have, as single substance and/or in mixtures, preferably melting points of from 30 to 200, preferably from 40 to 160°C. Preferred ancillary substances of this type are soluble in water, that is to say they generally have a solubility in water of at least 10, preferably at least 30, and, in particular, at least 40 g/100 ml of water at 20°C.

Fusible sugars C comprise, for example, monosaccharides such as glucose, mannose, galactose, arabinose, xylose, ribose and disaccharides such as sucrose, lactose, maltose. Sugar alcohols C preferred for the invention comprise xylitol, mannitol, sorbitol, isomalt, lactitol, erythritol, threitol, ribitol, arabitol and dulcitol. Preferred sugar alcohols of this type are described, for example, in EP-B 435 450. The term "sugar substitutes" for the purpose of the invention does not include sugar alcohols. Preferred sugar substitutes C comprise acesulfame, aspartame, saccharin, sodium cyclamate.

Further ancillary substances C comprise flavourings, sweeteners, lubricants, flow regulators, disintegrants and bulking agents such as, for example, starch and starch derivatives, cellulose and cellulose derivatives, polyethylenes.

The effervescent preparations obtainable according to the invention may contain the components in a wide variety of ratios of amounts; preferred effervescent preparations contain (in each case in parts by weight)

A: 5 to 95, preferably 10 to 80,
B: 5 to 95, preferably 40 to 60,
C: 1 to 60, preferably 15 to 30 (sugar, sugar alcohol, or sugar substitute) and, where appropriate,
1 to 50, preferably 5 to 15 (other ancillary substances).

The effervescent composition A preferably contains
30 to 70% by weight of CO_2 donor and
70 to 30% by weight of acidic component,
in each case based on A.

The melt of effervescent composition A (component) and fusible sugar and/or sugar alcohol and/or sugar substitute C can be prepared, for example, by adding

effervescent composition A (components) to a melt of sugar and/or sugar alcohol and/or sugar substitute C or by melting a mixture of effervescent composition A (components) and sugar and/or sugar alcohol and/or sugar substitute C.

However, the process according to the invention can also be carried out by contacting all components of the effervescent preparation with the molten sugar and/or sugar alcohol and/or sugar substitute for the purpose of dispersion, whether by premixing all components and heating together, or whether by melting sugar and/or sugar alcohol and/or sugar substitute and dispersing the remaining components (simultaneously or successively) in the melt. It is, of course, possible to use mixed forms of the process variants described.

The melt can be produced in virtually any suitable manner;
Thus, it is possible straightforwardly to use heatable stirred vessels. It is also possible to use a melt-granulation process as described, for example, in WO 92/6679. A preferred process is melt extrusion as described, for example, in EP-A 686 392. It is possible to employ for the extrusion commercially available single screw and twin-screw extruders. It is moreover possible to feed the starting materials to the extrusion via a weigh feeder. The melt temperature can be 30 to 200°C. The pressure can preferably be 2 to 200 bar, depending on the die orifice (preferably 0.5 to 5 mm) and the speed of rotation (preferably 5 to 400 revolutions/minute). The output can vary within wide limits, but is preferably 1 to 100 kg/hour. The extrudates are cooled where appropriate. After the comminution, they can be mixed with active substance B and, where appropriate, further ancillary substances C, and tabletted where appropriate.

Preferably neither water nor an organic solvent which is volatile under the processing conditions is employed in the process according to the invention, that is to say preferably water and solvent are absent from the process. In other words,: the process is precisely not that described in German Offenlegungsschrift 22 16 072 or in
Acta Pharm. Suec., 24, (2), 84, 1987
Drug Dev. Ind. Pharm. 13, (9-11), 1891-1913, 1987
Drug Dev. Ind. Pharm. 14, (13), 1791-98, 1988.

The process according to the invention can be carried out continuously or batchwise.

In the process according to the invention, component A(i) and/or A(ii) and, where appropriate, further effervescent preparation components are dispersed in the fusible sugar, sugar alcohol or sugar substitute C, that is to say the fusible component C forms a matrix in which A(i) and/or A(ii) and, where appropriate, further effervescent preparation components are embedded.

Thus the invention also relates to effervescent preparations consisting of

A. effervescent composition containing
   (i) CO_2 donor and
   (ii) acidic component,
B. pharmaceutical active substance and
C. - ancillary substance,

characterized in that ancillary substance C contains fusible sugar and/or sugar alcohol and/or sugar substitute, and component A(i) and/or A(ii) is dispersed in a matrix of fusible sugar and/or sugar alcohol and/or sugar substitute.

The percentage data in the following examples are based on weight in each case.

Examples

Example 1

Effervescent preparation consisting of separately extruded components A(i) and A(ii)

Extrudate I

Mannitol and sodium bicarbonate are mixed in the ratios indicated in the table. The mixture is processed in a twin-screw extruder (Leistriz Micro 27/40D) at a speed of rotation of 30 rpm and with a die diameter of 1 mm. The dies are arranged around the outer diameter of the screws. Mixing zones and die temperature are at 80°C. The extrudate is cooled on a cooling belt and then comminuted with an oscillating sieve.

Extrudate II

Mannitol, citric acid and sodium citrate are mixed and extruded and further processed as above.

	Extrudate I:	Extrudate II:
Mannitol	60%	60%
Sodium bicarbonate	40%	
Citric acid		6.7%
Sodium citrate		33.3%

Based on a single dose, 125 g of extrudate I and 150 mg of extrudate II are mixed with 500 mg of acetylsalicylic acid, 5 mg of aspartame and 30 mg of orange flavour and packed in a sachet.

Example 2

In analogy to Example 1, extrudate I and extrudate II are extruded at a temperature of 70°C, with a die diameter of 0.8 mm and a speed of rotation of 26 rpm.

	Extrudate I:	Extrudate II:
Xylitol	60%	60%
Sodium bicarbonate	40%	
Citric acid		40%

Based on a single dose, 125 mg of extrudate I and 150 mg of extrudate II are mixed with 500 mg of acetylsalicylic acid, 4 mg of saccharin and 30 mg of mandarin flavour and packed in a sachet.

Example 3

In analogy to Example 2, extrudate I and Extrudate II are extruded at a temperature of 60°C, with a die diameter of 1 mm and a speed of rotation of 35 rpm.

	Extrudate I:	Extrudate II:
Xylitol	30%	30%
Sodium bicarbonate	70%	
Citric acid		70%

Based on a single dose, 125 mg of each of extrudate I and II are mixed with 150 mg of ascorbic acid and 2.5 mg of chlorpheniramine maleate and packed in a sachet.

Example 4

In analogy to Example 2, extrudate I and extrudate II are extruded at a temperature of 60°C, with a die diameter of 2 mm and a speed of rotation of 35 rpm

	Extrudate I:	Extrudate II:
Isomalt	60%	
Xylitol		60%
Potassium bicarbonate	40%	
Ascorbic acid		40%

Based on a single dose, 125 mg of extrudate I and 250 mg of extrudate II are mixed with 500 mg of acetylsalicylic acid, 5 mg of saccharin, 2 mg of aspartame and 30 mg of orange flavour and packed in a sachet.

Example 5

In analogy to Example 1, extrudate I and extrudate II are extruded at a temperature of 60°C, with a die diameter of 1 mm and a speed of rotation of 35 rpm.

	Extrudate I:	Extrudate II:
Mannitol	60%	60%
Sodium bicarbonate	20%	
Calcium carbonate	20%	
Ascorbic acid		40%

Based on a single dose, in each case 1500 mg of extrudate I and 750 mg of extrudate II are mixed with 5 mg of aspartame and 10 mg of redcurrant flavour and packed in a sachet.

Example 6

A formulation with only one extruded component, namely A(ii)

Extrudate II from Example 2	1200 mg
Famotidine	10 mg
Sodium bicarbonate	400 mg
Sodium carbonate	100 mg
Magnesium stearate	20 mg

In analogy to Example 1, only the acid component is extruded, and the alkaline effervescent component and the active substance are mixed therewith. Subsequently, magnesium stearate is mixed in. This mixture is compressed to an effervescent tablet.

Example 7

Joint extrusion of A(i) and A(ii)

Xylitol	60%
Na citrate	14%
Sodium bicarbonate	23%
Citric acid	3%

Production process:

A) Extrusion in analogy to Example 1, or

B) Melt xylitol at about 120°C and meter and stir in the components successively. After cooling, the melt cake is comminuted.

Based on a single dose, in each case 600 mg of the resulting extrudate, 200 mg of acetylcysteine and 10 mg of lemon flavour are mixed. The resulting powder mixture is packed in a sachet.

Example 8

A mixture of 54% xylitol, 6% pseudoephedrine, 14% sodium citrate, 23% sodium bicarbonate and 3% citric acid is extruded in analogy to Example 1. The extrudate is comminuted and packaged.

Stability comparison of ASA-containing effervescent formulations

Determination of the degradation product salicylic acid (SA) after storage in packaging impermeable to water vapour at 25°C for 3 months

	Initial SA content	SA content after 3 months
ASA effervescent granules, flavoured*	0.02%	1.61%
ASA effervescent granules (extruded), flavoured[XX]	0.04%	0.18%
ASA effervescent tablet, flavoured*	0.3%	1.83%
ASA effervescent tablet, unflavoured*	0.17%	0.8%

* Granules are produced by conventional technology (comparative test)

xx According to the invention

Patent claims

1. Process for producing medicament-containing effervescent preparations consisting of

   A. effervescent composition containing
      (i) CO_2 donor and
      (ii) acidic component,
   B. pharmaceutical active substance and
   C. ancillary substance,

   characterized in that

   - at least one of the two components A(i) and A(ii) and, where appropriate, other effervescent preparation components are dispersed in molten C) sugar and/or sugar alcohol and/or sugar substitute, and the resulting mixture is tabletted where appropriate.

2. Process according to Claim 1, wherein

   - a melt consisting of component A(i) and/or A(ii) and C) fusible sugar, sugar alcohol and/or sugar substitute is comminuted during or after the cooling,

   - the comminuted product is mixed with active substance B, with component (i) or (ii), which is still missing where appropriate, of the effervescent composition A and, where appropriate, with further ancillary substances C and, where appropriate,

   - the resulting mixture is tabletted.

3. Process according to Claim 1, wherein an extruder is used for the melting.

4. Process according to Claim 1, wherein the pharmaceutical active substance B is selected from the group of analgesics, antacids, antiasthmatics/bronchospasmolytics, antibiotics, psychopharmaceuticals, antidiabetics, antiallergics/antihistamines, antihypotensives, antitussives, laxatives, mucolytics/expectorants, H2 blockers, local anaesthetics, antiemetics/prokinetics, lipid lowering agents, agents effective for migraine, sympathomimetics, vitamins, minerals.

5. Process according to Claim 1, wherein the temperature of the melt is 30 to 200°C.

6. Process according to Claim 1, wherein the temperature of the melt is 40 to 160°C.

7. Effervescent preparation consisting of

A. effervescent composition containing

(i) CO_2 donor and

(ii) acidic component,

B. pharmaceutical active substance and

C. ancillary substance,

characterized in that ancillary substance C contains fusible sugar and/or sugar alcohol and/or sugar substitute, and component A(i) and/or A(ii) is dispersed in a matrix of fusible sugar and/or sugar alcohol and/or sugar substitute.

Effervescent preparations

Abstract

Medicament-containing effervescent preparations are particularly stable on storage when they contain fusible sugar, sugar alcohol and/or sugar substitute.

COMBINED DECLA ION AND POWER OF ATTORNEY	ATTORNEY DOCKET NO Le A 32 842

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought
on the invention entitled

"EFFERVESCENT PREPARATIONS"

the specification of which is attached hereto,

or was filed on **May 3, 1999**

as a PCT Application Serial No. **PCT/EP99/02969**

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s), the priority(ies) of which is/are to be claimed:

198 22 036.7 (Number)	**Germany** (Country)	**May 15, 1998** (Month/Day/Year Filed)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose the material information as defined in Title 37, Code of Federal Regulations, §1.56 which occured between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all busin n the Patent and Trademark Office connec therewith:

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